# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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|---|---|---|
| 2003946-0024(PITA) | | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US 03/00390 | 08.01.2003 | 08.01.2002 |

International Patent Classification (IPC) or both national classification and IPC
C07D303/36

Applicant
EISAI CO. LTD. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 15 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 25.07.2003 | 05.02.2004 |

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/00390

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

| | |
|---|---|
| 1-112 | as originally filed |
| 3a | received on 21.11.2003 with letter of 19.11.2003 |

**Claims, Numbers**

| | |
|---|---|
| 1-7, 10-14, 16-18, 38-55, 57, 58, 60-82 | received on 21.11.2003 with letter of 19.11.2003 |

**Drawings, Sheets**

| | |
|---|---|
| 1/1 | as originally filed |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 68-70

   because:

   ☒ the said international application, or the said claims Nos. 68-70 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-67 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-67 |
| Industrial applicability (IA) | Yes: | Claims | 1-67 |
| | No: | Claims | |

2. Citations and explanations

see separate sheet

SECTION III

1). Claims 68-70 relate to the treatment of human and/or animal bodies. According to Rule 67(1)(iv) an examination is not required for such claims.

SECTION V

2). Relevant prior art is represented by:

D1: ELOFSSON M ET AL: 'TOWARDS SUBUNIT-SPECIFIC PROTEASOME INHIBITORS: SYNTHESIS AND EVALUATION OF PEPTIDE ALPHA',BETA'-EPOXYKETONES' CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 6, no. 11, 1995, pages 811-822, XP001002198 ISSN: 1074-5521 cited in the application

D2: SIN N ET AL: 'Total synthesis of the potent proteasome inhibitor epoxomicin: a useful tool for understanding proteasome biology' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 15, 2 August 1999 (1999-08-02), pages 2283-2288, XP004174176 ISSN: 0960-894X cited in the application

D3: ADAMS JULIAN ET AL: 'Proteasome inhibitors: A novel class of potent and effective antitumor agents' CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 59, no. 11, 1 June 1999 (1999-06-01), pages 2615-2622, XP002168152 ISSN: 0008-5472

D4: IQBAL M ET AL: 'POTENT ALPHA-KETOCARBONYL AND BORONIC ESTER DERIVED INHIBITORS OF PROTEASOME' BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 3, 1996, pages 287-290, XP000791145 ISSN: 0968-0896

D5: MOMOSE, ISAO ET AL: 'Tyropeptins A and B, new proteasome inhibitors produced by Kitasatospora sp. MK993-dF2. I. Taxonomy, isolation, physico-chemical properties and biological activities' JOURNAL OF ANTIBIOTICS (2001), 54(12), 997-1003 , XP002252184

D6: HARDING, CLIFFORD V. ET AL: 'Novel dipeptide aldehydes are proteasome inhibitors and block the MHC-I antigen-processing pathway' JOURNAL OF IMMUNOLOGY (1995), 155(4), 1767-75 , XP002252185

D7: GARDNER, ROBERT C. ET AL: 'Characterization of peptidyl boronic acid

inhibitors of mammalian 20 S and 26 S proteasomes and their inhibition of proteasomes in cultured cells' BIOCHEMICAL JOURNAL (2000), 346(2), 447-454 , XP002252186

D8: SUN, JIAZHI ET AL: 'CEP1612, a dipeptidyl proteasome inhibitor, induces p21WAF1 and p27KIP1 expression and apoptosis and inhibits the growth of the human lung adenocarcinoma A-549 in nude mice' CANCER RESEARCH (2001), 61(4), 1280-1284 , XP002252187

D9: WO 96 13266 A (PROSCRIPT, INC.) 9 May 1996 (1996-05-09)

D10: WO 95 24914 A (MYCOGENICS, INC.) 21 September 1995 (1995-09-21)

D11: WO 02 096933 A (NOVARTIS AG) 5 December 2002 (2002-12-05)

D12: WO 03 033506 A (KYORIN PHARMACEUTICALS, CO., LTD.) 24 April 2003 (2003-04-24)

3). Although the amendments carried out by the applicant seem to incorporate now subject-matter which was not disclosed in the application as originally filed, an opinion with regard to novelty and inventive step will be given as if the current claims were supported by the description (see for example, replacement for the sum of x, y and z is 0-6 by 2-6; there is apparently no fall-back position for such values).

4). In view of the applicant's analysis provided with his letter of 19.11.2003, it appears that the set of claims is novel vis-à-vis the cited prior art.

5). The problem underlying the current application appears to be the provision of further derivatives which can inhibit proteasomes (see page 2, last line).

An inventive step cannot be acknowledged in view of D9, since this document clearly discloses compounds having the same properties as those of the current application (see page 4, lines 11-12).
The applicant has clearly disclaimed some compounds of this document (see letter of 19.11.2003). Hence, if a disclaimer can render a claim novel, it cannot be used to render it inventive.

Moreover, the wording of the claims contains unlimited terms like "optionally substituted", "aryl", "heterocyclyl", "alicyclic", "aliphatic", "protecting group", "prodrug" and derivatives thereof which lead to an infinite number of compounds which cannot

inherently represent a solution to the given problem.

An inventive step is not acknowledged.

6). There is no objection with regard to industrial applicability.

are useful, for example, for the treatment of various disorders involving proteasome activity, including, for example, cancer, immune or inflammatory disorders, or HIV.

## BRIEF DESCRIPTION OF THE DRAWING

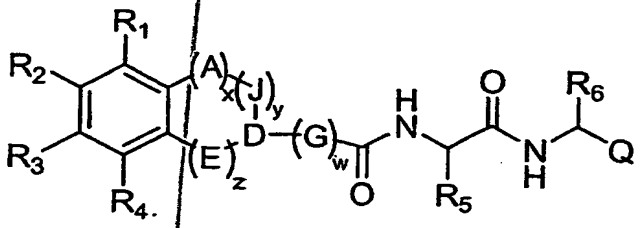
[0006] Figure 1 is a graphical representation depicting comparative human breast carcinoma cell growth inhibition of Paclitaxel and exemplary inventive compounds.

## DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS OF THE INVENTION

[0007] As discussed above, the demonstrated antitumor and anti-inflammatory activity of the natural products epoxomicin and eponemycin, as well as their ability to inhibit the 20S proteasome, has led to increased interest in the synthesis and biological investigation of these compounds and epoxyketones generally. In recognition of the need to further develop the therapeutic potential of this class of compounds, the present invention provides novel epoxomicin and eponemycin analogs. In certain embodiments, the compounds of the present invention can be used for the treatment of cancer and inflammatory disorders. More generally, in certain other embodiments, the compounds of the invention act as proteasome inhibitors.

[0008] *1) General Description of Compounds of the Invention*

The compounds of the invention include compounds of the general formula (I) as further defined below:



(I)

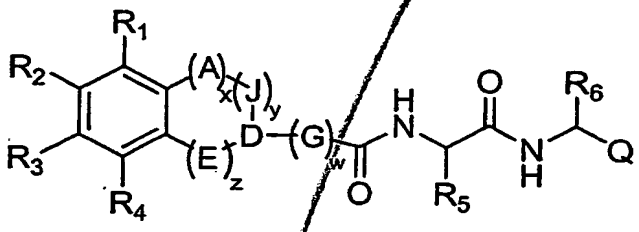
and pharmaceutically acceptable derivatives thereof;

wherein each occurrence of A, J, E, D or G is independently absent, $CR_A$, $CR_AR_B$, C=O, O, S, $NR_A$, or N, wherein each occurrence of $R_A$ and $R_B$ is independently hydrogen, a protecting group, or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety;

A and J, J and D, D and E, and D and G are each independently linked by a single or double bond as valency permits;

## CLAIMS

1. A compound having the structure (I):



(I)

and pharmaceutically acceptable derivatives thereof;

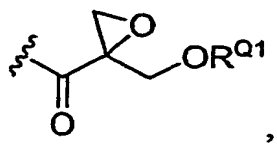
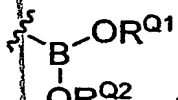
wherein each occurrence of A, J, E, D or G is independently $CR_A$, $CR_AR_B$, C=O, O, S, $NR_A$, or N, wherein each occurrence of $R_A$ and $R_B$ is independently hydrogen, a protecting group, or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety;

A and J, J and D, D and E, and D and G are each independently linked by a single or double bond as valency permits;

w, x, y and z are each independently 0, 1, 2, 3, 4, 5 or 6, but the sum of x, y and z is 2-6;

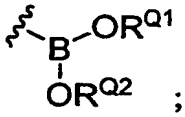
$R_1$, $R_2$, $R_3$ and $R_4$ are each independently hydrogen, halogen, -CN, $-OR_C$, $-SR_C$, $-NR_CR_D$, $-(C=O)R_C$ or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, wherein each occurrence of $R_C$ and $R_D$ is independently hydrogen, a protecting group, or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or $R_C$ and $R_D$, taken together, form a heteroalicyclic or heteroaryl moiety; or wherein any two adjacent groups $R_1$, $R_2$, $R_3$ and $R_4$, taken together, form an alicyclic or heteroalicyclic moiety, or an aryl or heteroaryl moiety;

$R_5$ and $R_6$ are each independently an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety; and

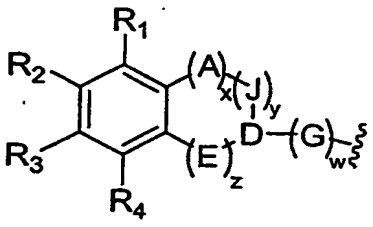
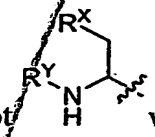
Q is an epoxycarbonyl moiety having the structure:  , or a boron-containing moiety having the structure:  ; wherein wherein $R^{Q1}$ and $R^{Q2}$ are each independently hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or an oxygen protecting group, or $R^{Q1}$ and $R^{Q2}$, taken together, form a

heteroalicyclic moiety; or, when Q is an epoxyxarbonyl moiety, $R^{Q1}$ may also be a prodrug moiety;

with the proviso that, when Q is a boron-containing moiety having the structure:

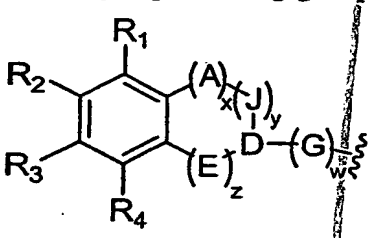
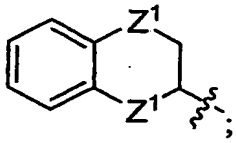


; then

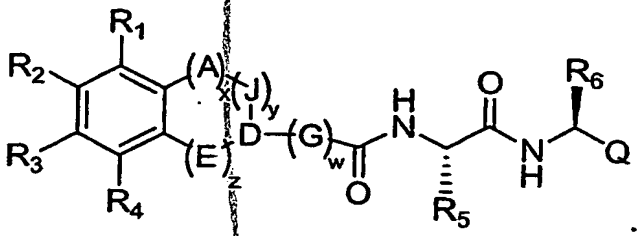
(i)  is not  where $R^X$ is aryl or heteroaryl and $R^Y$ is aryl, heterocyclyl, aylalkylcarbonyl or heterocyclylalkylcarbonyl;

(ii) if D is N or CH, and (a) w is 0, or (b) w is 1 and G is $-CH(OH)-CH_2-$, then neither occurrence of J nor E attached to D, nor the occurrence of A attached to D when y is 0, is a nitrogen atom substituted with hydrogen or a nitrogen protecting group typically employed in peptide synthesis;

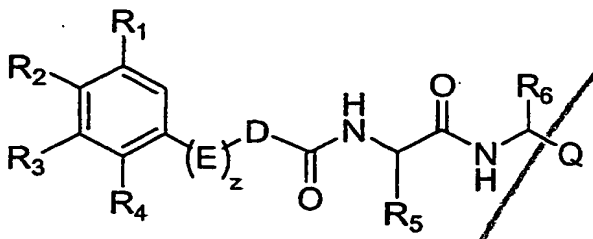
(iii) when w is other than 0, then the occurrence of G attached to D is not N or CH substituted with $-NR^xR^y$ where $R^x$ is hydrogen or alkyl and $R^y$ is hydrogen or a nitrogen protecting group typically employed in peptide synthesis; and/or

(iv)  is not  ; wherein $Z^1$ is O or S.

2. The compound of claim 1, wherein the compound has the structure:



3. A compound not comprising more than two consecutive α-amino acid residues having the structure:



and pharmaceutically acceptable derivatives thereof;

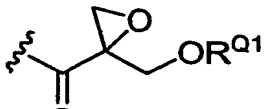
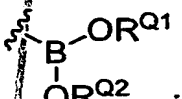
wherein each occurrence of E and D is independently absent, $CR_A$, $CR_AR_B$, C=O, O, S, $NR_A$, or N, wherein each occurrence of $R_A$ and $R_B$ is independently hydrogen, a protecting group, or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety;

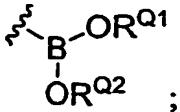
D and E are each independently linked by a single or double bond as valency permits;

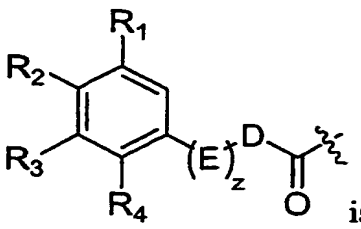
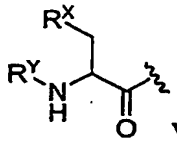
z is 0, 1, 2, 3, 4, 5 or 6;

$R_1$, $R_2$, $R_3$ and $R_4$ are each independently hydrogen, halogen, -CN, $-OR_C$, $-SR_C$, $-NR_CR_D$, $-(C=O)R_C$ or an aliphatic, Page 114 of 129 atic, heteroalicyclic, aryl or heteroaryl moiety, wherein each occurrence of $R_C$ and $R_D$ is independently hydrogen, a protecting group, or an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or $R_C$ and $R_D$, taken together, form a heteroalicyclic or heteroaryl moiety; or wherein any two adjacent groups $R_1$, $R_2$, $R_3$ and $R_4$, taken together, form an alicyclic or heteroalicyclic moiety, or an aryl or heteroaryl moiety;

$R_5$ and $R_6$ are each independently an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety; and

Q is an epoxycarbonyl moiety having the structure:  , or a boron-containing moiety having the structure:  ; wherein wherein $R^{Q1}$ and $R^{Q2}$ are each independently hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or an oxygen protecting group, or $R^{Q1}$ and $R^{Q2}$, taken together, form a heteroalicyclic moiety; or, when Q is an epoxyxarbonyl moiety, $R^{Q1}$ may also be a prodrug moiety;

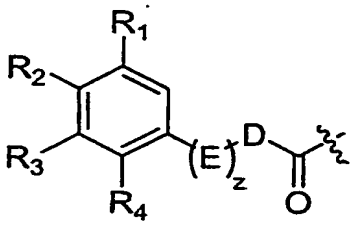
with the proviso that, when Q is a boron-containing moiety having the structure:  ; then

(i)  is not  where $R^X$ is aryl or heteroaryl and $R^Y$ is aryl, heterocyclyl, aylalkylcarbonyl or heterocyclylalkylcarbonyl;

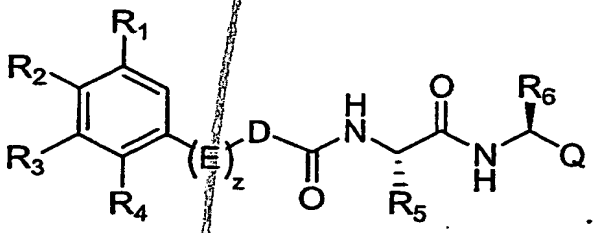
(ii) at least one of $R_1$-$R_4$ is not H;

(iii) if $-(E)_z$-D- is $-CH_2-$ and one of $R_1$-$R_4$ is MeO- or halogen, then the others are not each hydrogen;

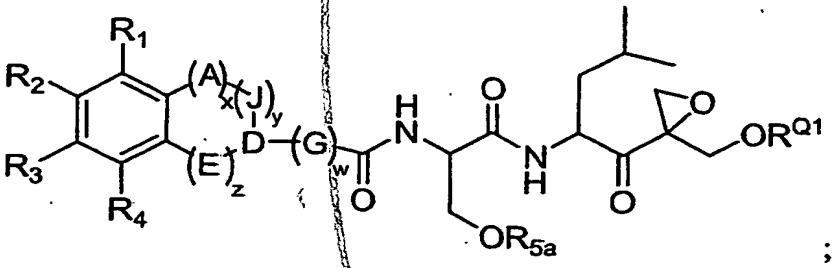
(iv) the occurrence of E attached to phenyl, or D when z is 0, is not N or CH substituted with $-NR^xR^y$ where $R^x$ is hydrogen or alkyl and $R^y$ is hydrogen or a nitrogen protecting group typically employed in peptide synthesis; and/or

(v)  is not a nitrogen protecting group typically employed in peptide synthesis.

4. The compound of claim 3, wherein the compound has the structure:



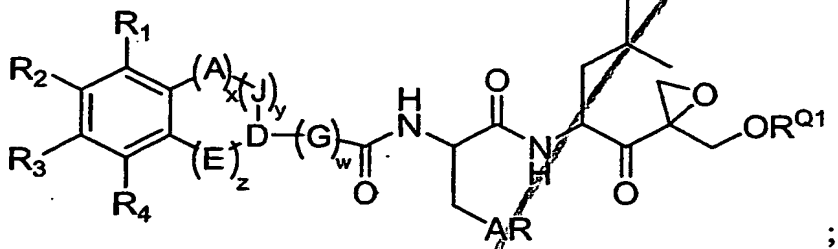
5. The compound of claim 1, wherein $R_5$ is $-CH_2OR_{5a}$ and the compound has the structure:



;

wherein $R_{5a}$ is hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, an oxygen protecting group or a prodrug moiety.

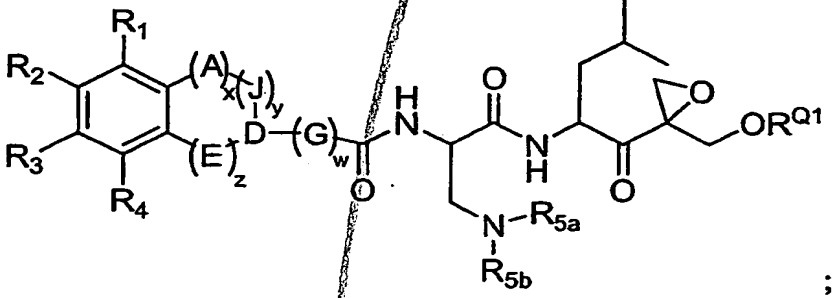
6. The compound of claim 1, wherein $R_5$ is aryl or heteroaryl and the compound has the structure:



;

wherein AR is an aryl or heteroaryl moiety.

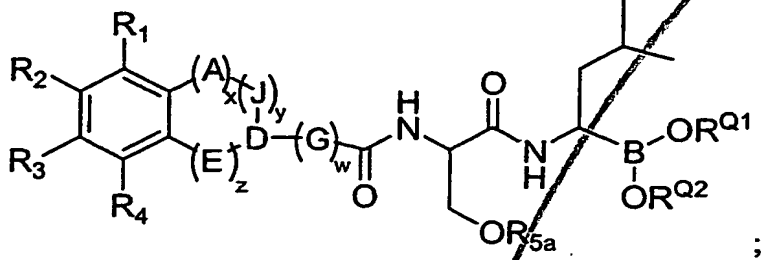
7. The compound of claim 1, wherein $R_5$ is $-CH_2NR_{5a}R_{5b}$ or heteroaryl and the compound has the structure:



;

wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, a nitrogen protecting group, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or a prodrug , or $R_{5a}$ and $R_{5b}$, taken together, form a heteroalicyclic or heteroaryl moiety.

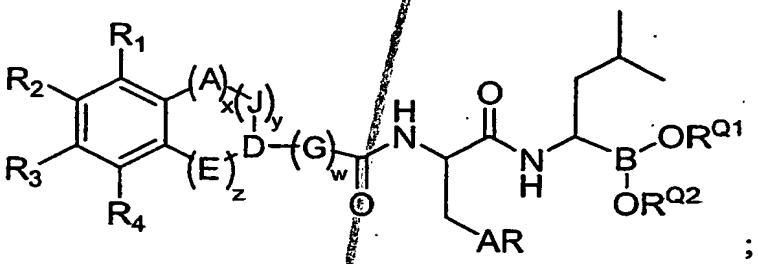
10. The compound of claim 1, wherein $R_5$ is $-CH_2OR_{5a}$ and the compound has the structure:



;

wherein $R_{5a}$ is hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, an oxygen protecting group or a prodrug moiety.

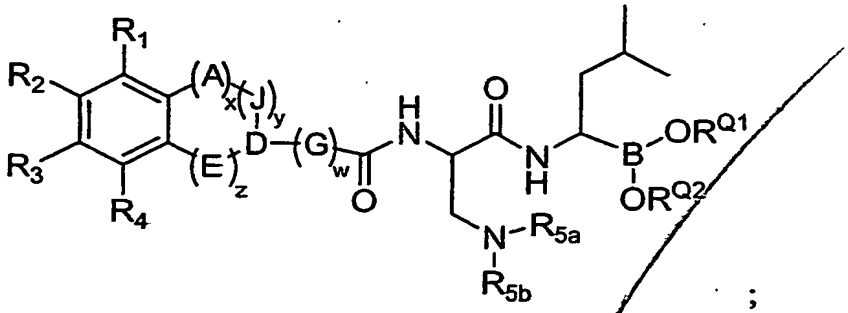
11. The compound of claim 1, wherein $R_5$ is aryl or heteroaryl and the compound has the structure:



;

wherein AR is an aryl or heteroaryl moiety.

12. The compound of claim 1, wherein $R_5$ is $-CH_2NR_{5a}R_{5b}$ or heteroaryl and the compound has the structure:



;

wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, a nitrogen protecting group, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or a prodrug , or $R_{5a}$ and $R_{5b}$, taken together, form a heteroalicyclic or heteroaryl moiety.

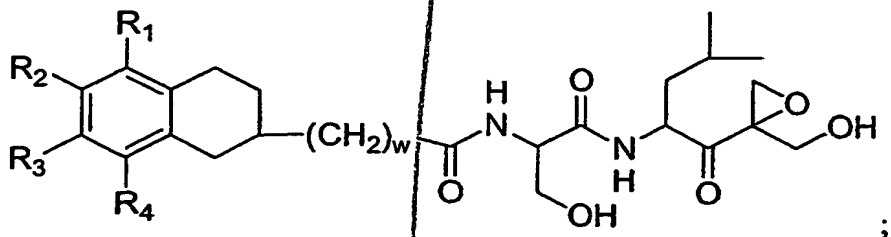
13. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x, y and z are each 1, and A, J, D, and E are each $CH_2$.

14. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein w, x and y are each 0.

16. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein G is $CH_2$ and w is 0, 1, or 2.

17. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x, y and z are each 1; A, J, D, and E are each $CH_2$; G is $CH_2$ and w is 0, 1, or 2.

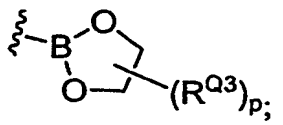
18. The compound of claim 1, wherein x, y and z are each 1; A, J, D, and E are each $CH_2$ and the compound has the structure:



;



As filed



wherein $R^{Q3}$ is lower alkyl and p is an integer from 0-4.

38. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x, y and z are each 1 and A-J-D-E together represent $-CH_2-CH_2-CH_2-CH_2-$.

39. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x is 0, y and z are each 1, and J-D-E together represent $-CH_2-CH_2-CH_2-$.

40. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x is 0, z is 0 and E is absent and J-D together represents $-CH_2-CH_2-$.

41. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x, y and z are each 1 and A-J-D-E together represent –N=CH-CH=N-.

42. The compound of any one of claims 1, 2, 5-7, and 10-12, wherein x, y and z are each 1 and A-J-D-E together represent $-CH_2-CH_2-CH_2-CH_2-$ and G is $CH_2$ and w is 0, 1 or 2.

43. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$, $R_2$, $R_3$ and $R_4$ are each independently hydrogen, halogen, protected or unprotected hydroxyl, protected or unprotected thiol, protected or unprotected amino, alkyl, alkoxy, thioalkyl, mono-or di-substituted alkylamino, or wherein any two adjacent groups $R_1$, $R_2$, $R_3$ or $R_4$, taken together are a cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety,

whereby each of the alkyl moieties is independently substituted or unsubstituted, linear or branched, cyclic or acyclic, and each of the aryl and heteroaryl moieties is independently substituted or unsubstituted.

44. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$, $R_2$, $R_3$ and $R_4$ are each independently hydrogen or lower alkoxy.

45. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$, $R_2$, $R_3$ and $R_4$ are each independently hydrogen or methoxy.

46. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$, $R_2$, $R_3$ and $R_4$ are each methoxy.

47. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$ is hydrogen and each of $R_2$, $R_3$ and $R_4$ are independently lower alkoxy.

48. The compound of any one of claims 1-7, 10-12 and 18-23, wherein $R_1$ is hydrogen and each of $R_2$, $R_3$ and $R_4$ are methoxy.

49. The compound of any one of claims 1-4, wherein $R_5$ is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, $C_{1-6}OR_{5a}$, $C_{1-6}NR_{5a}R_{5b}$, aryl or heteroaryl; wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, $-C(NH_2)=N(NO_2)$, $-C(=O)OR_{5c}$, $-C(=O)R_{5c}$ or a protecting group; wherein $R_{5c}$ is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl.

50. The compound of any one of claims 1-4, wherein $R_5$ is alkyl, cycloalkyl, $-CH_2OR_{5a}$, $-CH_2NR_{5a}R_{5b}$, $-CH_2$aryl or $-CH_2$heteroaryl; wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, $-C(NH_2)=N(NO_2)$, $-C(=O)OR_{5c}$, $-C(=O)R_{5c}$ or a protecting group; wherein $R_{5c}$ is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl.

51. The compound of any one of claims 1-4, wherein $R_5$ is alkyl, cycloalkyl, $CH_2OR_{5a}$, $CH_2NR_{5a}R_{5b}$ or substituted or unsubstituted $-CH_2Ph$; wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, $-C(NH_2)=N(NO_2)$, $-C(=O)OR_{5c}$, $-C(=O)R_{5c}$ or a protecting group; wherein $R_{5c}$ is hydrogen, alkyl, alkenyl, alkynyl, aryl or heteroaryl.

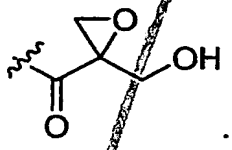
52. The compound of any one of claims 1-4, wherein $R_5$ is $-CH_2OH$ or benzyl.

53. The compound of any one of claims 1-4, wherein $R_6$ is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl or heteroaryl.

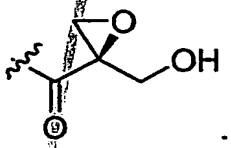
54. The compound of any one of claims 1-4, wherein $R_6$ is lower alkyl or aryl.

55. The compound of any one of claims 1-4, wherein $R_6$ is $-CH_2CH(CH_3)_2$.

57. The compound of claim 1, 2, 3 or 4, wherein Q has the structure:

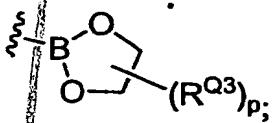


58. The compound of claim 57, wherein Q has the structure:



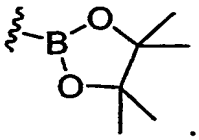
60. The compound of claim 1, 2, 3 or 4, wherein Q is $-B(OH)_2$.

61. The compound of claim 1, 2, 3 or 4, wherein Q has the structure:



wherein $R^{Q3}$ is lower alkyl and p is an integer from 0-4.

62. The compound of claim 61, wherein Q has the structure:



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63. A pharmaceutical composition comprising a compound of any one of claims 1-7, 10-12 and 18-35; and

a pharmaceutically acceptable carrier or diluent, and optionally further comprising an additional therapeutic agent.

64. The pharmaceutical of claim 63 wherein the compound is present in an amount effective to exert an antiproliferative and/or anticancer effect.

65. The pharmaceutical of claim 63 wherein the compound and the additional therapeutic agent are present in an amount effective to exert an antiproliferative and/or anticancer effect.

66. The pharmaceutical of claim 63 wherein the compound is present in an amount effective to exert an anti-inflammatory effect.

67. The pharmaceutical of claim 63 wherein the compound and the additional therapeutic agent are present in an amount effective to exert an anti-inflammatory effect.

68. A method for treating cancer comprising:

administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-7, 10-12 and 18-35; and

optionally further administering an additional therapeutic agent.

69. The method of claim 68, wherein the method is used to treat prostate, breast, colon, bladder, cervical, skin, testicular, kidney, ovarian, stomach, brain, liver, pancreatic or esophageal cancer or lymphoma, leukemia, or multiple myeloma.

70. The method of claim 68, wherein the cancer is a solid tumor.

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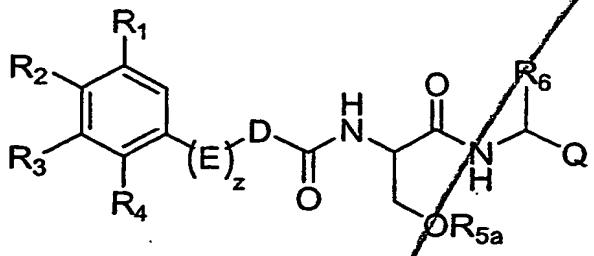
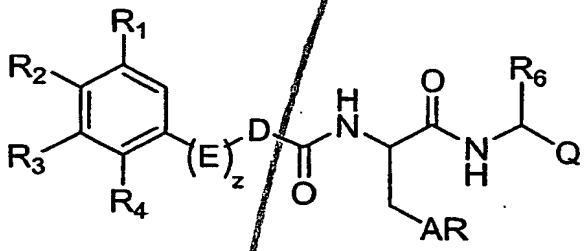
71. The compound of claim 3 having the structure:



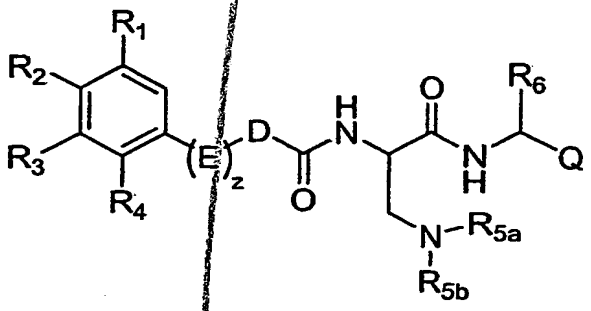
wherein $R_{5a}$ is hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, an oxygen protecting group or a prodrug moiety.

72. The compound of claim 3 having the structure:



wherein AR is an aryl or heteroaryl moiety.

73. The compound of claim 3 having the structure:



wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, a nitrogen protecting group, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or a prodrug , or $R_{5a}$ and $R_{5b}$, taken together, form a heteroalicyclic or heteroaryl moiety.

74. The compound of claim 3 having the structure:

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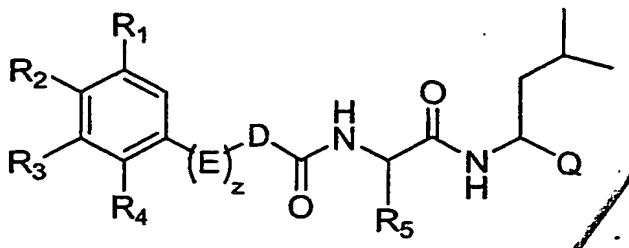
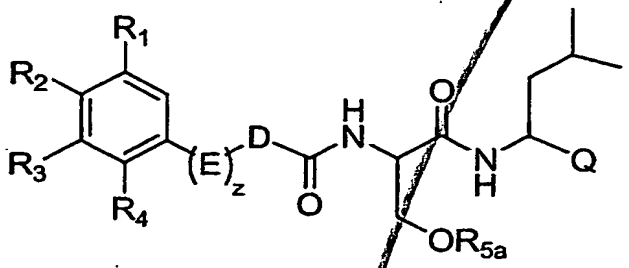
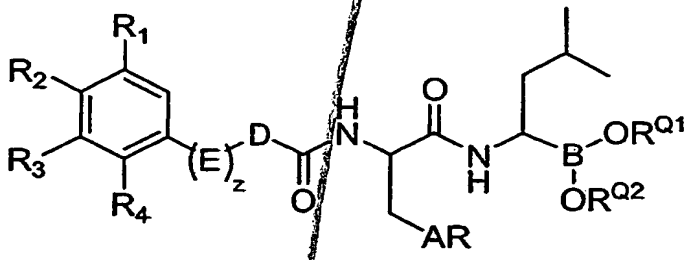


75. The compound of claim 3 having the structure:



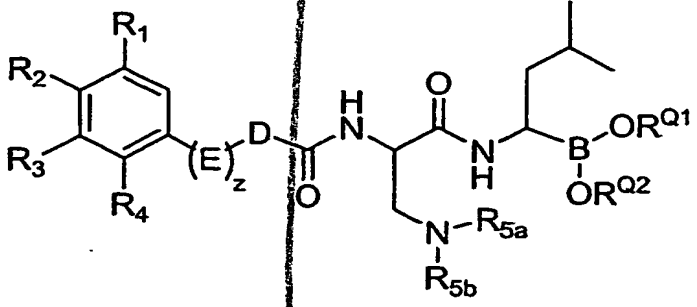
wherein $R_{5a}$ is hydrogen, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, an oxygen protecting group or a prodrug moiety.

76. The compound of claim 3 having the structure:



wherein AR is an aryl or heteroaryl moiety.

77. The compound of claim 3 having the structure:

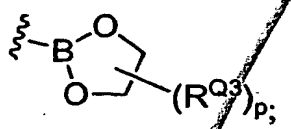


wherein $R_{5a}$ and $R_{5b}$ are each independently hydrogen, a nitrogen protecting group, an aliphatic, alicyclic, heteroaliphatic, heteroalicyclic, aryl or heteroaryl moiety, or a prodrug , or $R_{5a}$ and $R_{5b}$, taken together, form a heteroalicyclic or heteroaryl moiety.

78. The compound of any one of claims 2, 3 and 71-77, wherein D is absent and z is 0.

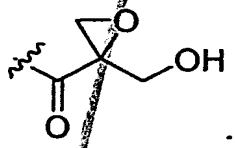
79. The compound of any one of claims 2, 3 and 71-77, wherein Q is $-B(OH)_2$.

80. The compound of any one of claims 2, 3 and 71-77, wherein Q is a moiety having the structure:

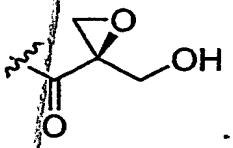


wherein $R^{Q3}$ is lower alkyl and p is an integer from 0-4.

81. The compound of any one of claims 2, 3 and 71-77, wherein Q is a moiety having the structure:



82. The compound of claim 81, wherein Q is a moiety having the structure:



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